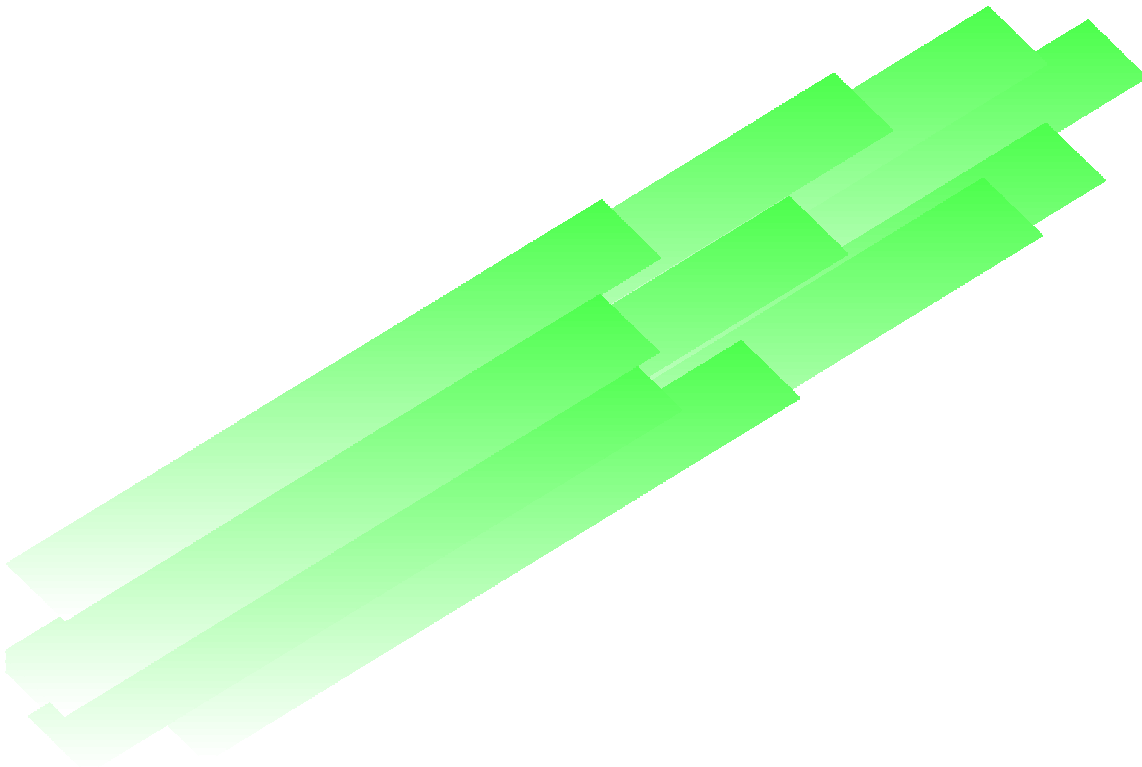


# **Guidance for Industry**

## **Labeling Guidance for Itraconazole Capsules**



**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
October 1998  
OGD-L-31**

# Guidance for Industry

## Labeling Guidance for Itraconazole Capsules

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# **GUIDANCE FOR INDUSTRY<sup>1</sup>**

## **Labeling Guidance for Itraconazole Capsules**

### **I. INTRODUCTION**

This guidance describes the recommended labeling to comply with 21 CFR 314.94(a)(8)(iv) for an abbreviated new drug application. The basis of this guidance is the approved labeling of the reference listed drug (SPORANOX®; Janssen Pharmaceutica Research Foundation; 20-083/S-019; Approved August 6, 1997; Revised February 1997). Differences between the reference listed drug and this guidance may exist and may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, or omission of an indication or other aspects of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act.

### **II. LABELING**

#### **ITRACONAZOLE CAPSULES**

##### **Rx Only**

#### **WARNINGS**

Coadministration of terfenadine, astemizole, and cisapride with itraconazole is contraindicated. Itraconazole is a potent inhibitor of the cytochrome P450 3A enzyme system and may raise plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including death, ventricular tachycardia, and torsades de pointes have occurred in patients taking itraconazole concomitantly with terfenadine or cisapride, which are metabolized by the cytochrome P450 3A system. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.

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<sup>1</sup>This guidance has been prepared by the Office of Generic Drugs, Division of Labeling and Program Support in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the development of labeling for an abbreviated new drug application. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

## DESCRIPTION

Itraconazole is a synthetic triazole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. Itraconazole is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1. It may be represented chemically as (±)-1-*sec*-Butyl-4-[*p*-[4-[*p*-[(2*R*\*,4*S*\*)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ<sup>2</sup>-1,2,4-triazolin-5-one. Itraconazole has a molecular formula of C<sub>35</sub>H<sub>38</sub>Cl<sub>2</sub>N<sub>8</sub>O<sub>4</sub> and a molecular weight of 705.65. The structural formula is as follows:

[INSERT STRUCTURAL FORMULA HERE]

Each capsule, for oral administration, contains 100 mg of itraconazole. In addition, each capsule contains the following inactive ingredients:

[Please note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance).]

## CLINICAL PHARMACOLOGY

### Microbiology:

Mechanism of Action: *In vitro* studies have demonstrated that itraconazole inhibits the cytochrome P-450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

Activity in vitro and in vivo: Itraconazole exhibits *in vitro* activity against *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Histoplasma duboisii*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Candida albicans* and *Cryptococcus neoformans*. Itraconazole also exhibits varying *in vitro* activity against *Sporothrix schenckii*, *Trichophyton* spp., *Candida krusei*, and other *Candida* spp. The bioactive metabolite, hydroxyitraconazole, has not been evaluated against *Histoplasma capsulatum* and *Blastomyces dermatitidis*. Correlation between *in vitro* minimum inhibitory concentration (MIC) results and clinical outcome has yet to be established for azole antifungal agents.

Itraconazole administered orally was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Fungistatic activity has been demonstrated against disseminated fungal infections caused by *Blastomyces dermatitidis*, *Histoplasma duboisii*, *Aspergillus fumigatus*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

Itraconazole administered at 2.5 mg/kg and 5 mg/kg via the oral and parenteral routes increased survival rates and sterilized organ systems in normal and immunosuppressed guinea pigs with disseminated *Aspergillus fumigatus* infections. Oral itraconazole administered daily at 40 mg/kg and 80 mg/kg increased survival rates in normal rabbits with disseminated disease and immunosuppressed rats with pulmonary *Aspergillus fumigatus* infection, respectively. Itraconazole has demonstrated antifungal activity in a variety of animal models infected with *Candida albicans* and other *Candida* species.

*In vivo* studies suggest that the activity of amphotericin B may be suppressed by azole antifungal therapy. As with other azoles, itraconazole inhibits the <sup>14</sup>C-demethylation step in the synthesis of ergosterol, a cell wall component of fungi. Ergosterol is the active site for amphotericin B. In one study the antifungal activity of amphotericin B against *Aspergillus fumigatus* infections in mice was inhibited by ketoconazole therapy. The clinical significance of test results obtained in this study is unknown.

Several *in vitro* studies have reported that some fungal clinical isolates, including *Candida* species, with reduced susceptibility to one azole antifungal agent may also be less susceptible to other azole derivatives. The finding of cross-resistance is dependent upon a number of factors, including the species evaluated, its clinical history, the particular azole compounds compared and the type of susceptibility test that is performed. The relevance of these *in vitro* susceptibility data to clinical outcome remains to be elucidated.

#### **Pharmacokinetics and Metabolism:**

**NOTE:** The plasma concentrations reported below were measured by high performance liquid chromatography (HPLC) specific for itraconazole. When itraconazole in plasma is measured by a bioassay, values reported are approximately 3.3 times higher than those obtained by HPLC due to the presence of the bioactive metabolite, hydroxyitraconazole. (See CLINICAL PHARMACOLOGY - Microbiology)

The pharmacokinetics of itraconazole after intravenous administration and its absolute oral bioavailability from an oral solution were studied in a randomized cross-over study using six healthy male volunteers. The observed absolute oral bioavailability of itraconazole was 55%.

The oral bioavailability of itraconazole is maximal when itraconazole capsules are taken with a full meal. The pharmacokinetics of itraconazole were studied using six healthy male volunteers who received, in a cross-over design, single 100 mg doses of itraconazole as a polyethylene glycol capsule, with or without a full meal. The same six volunteers also received 50 mg or 200 mg with a full meal in a cross-over design. In this study, only itraconazole plasma concentrations were measured. Presented in the table below are the respective pharmacokinetic parameters for itraconazole:

	50 mg (fed)	100 mg (fed)	100 mg (fasted)	200 mg (fed)
$C_{\max}$ (ng/mL)	$45 \pm 16^*$	$132 \pm 67$	$38 \pm 20$	$289 \pm 100$
$T_{\max}$ (hours)	$3.2 \pm 1.3$	$4.0 \pm 1.1$	$3.3 \pm 1.0$	$4.7 \pm 1.4$
$AUC_{0-\infty}$ (ng·h/mL)	$567 \pm 264$	$1899 \pm 838$	$722 \pm 289$	$5211 \pm 2116$

\* mean  $\pm$  standard deviation

Doubling the itraconazole dose results in approximately a three-fold increase in the itraconazole plasma concentrations.

Values given in the table below represent data from a cross-over pharmacokinetics study in which 27 healthy male volunteers each took a single 200 mg dose of itraconazole with or without a full meal:

	Itraconazole		Hydroxyitraconazole	
	Fed	Fasted	Fed	Fasted
$C_{\max}$ (ng/mL)	$239 \pm 85^*$	$140 \pm 65$	$397 \pm 103$	$286 \pm 101$
$T_{\max}$ (hours)	$4.5 \pm 1.1$	$3.9 \pm 1.0$	$5.1 \pm 1.6$	$4.5 \pm 1.1$
$AUC_{0-\infty}$ (ng·h/mL)	$3423 \pm 1154$	$2094 \pm 905$	$7978 \pm 2648$	$5191 \pm 2489$
$t_{1/2}$ (hours)	$21 \pm 5$	$21 \pm 7$	$12 \pm 3$	$12 \pm 3$

\* mean  $\pm$  standard deviation

Absorption of itraconazole under fasted conditions in individuals with relative or absolute achlorhydria, such as patients with AIDS or volunteers taking gastric acid secretion suppressors (e.g.,  $H_2$  inhibitors), was increased when itraconazole was administered with a cola beverage. Eighteen males with AIDS received single 200 mg doses of itraconazole under fasted conditions with 8 ounces of water or 8 ounces of a cola beverage in a crossover design. The absorption of itraconazole was increased when itraconazole capsules were coadministered with a cola beverage with  $AUC_{0-24}$  and  $C_{\max}$  increasing  $75 \pm 121\%$  and  $95 \pm 128\%$ , respectively. Thirty healthy males received single 200 mg doses of itraconazole capsules under fasted conditions either 1) with water; 2) with water, after ranitidine 150 mg bid for 3 days; or 3) with cola, after ranitidine 150 mg bid for 3 days. When itraconazole was administered after ranitidine pretreatment, itraconazole was absorbed to a lesser extent than when itraconazole was administered alone, with decreases in  $AUC_{0-24}$  and  $C_{\max}$  of  $39 \pm 37\%$  and  $42 \pm 39\%$ , respectively. When itraconazole capsules were administered with cola after ranitidine pretreatment, itraconazole absorption was comparable to

that observed when itraconazole was administered alone.

Steady-state concentrations were reached within 15 days following oral doses of 50 mg to 400 mg daily. Values given in the table below are data at steady-state from a pharmacokinetics study in which 27 healthy male volunteers took 200 mg itraconazole bid (with a full meal) for 15 days:

	Itraconazole	Hydroxyitraconazole
C <sub>max</sub> (ng/mL)	2282 ± 514*	3488 ± 742
C <sub>min</sub> (ng/mL)	1855 ± 535	3349 ± 761
T <sub>max</sub> (hours)	4.6 ± 1.8	3.4 ± 3.4
AUC <sub>0-12h</sub> (ng·h/mL)	22569 ± 5375	38572 ± 8450
t <sub>1/2</sub> (hours)	64 ± 32	56 ± 24

\*mean ± standard deviation

Results of the pharmacokinetics study suggest that itraconazole may undergo saturation metabolism with multiple dosing.

The plasma protein binding of itraconazole is 99.8% and that of hydroxyitraconazole is 99.5%. Following intravenous administration, the volume of distribution of itraconazole averaged 796 ± 185 L.

Itraconazole is extensively metabolized resulting in the formation of several metabolites including hydroxyitraconazole, the major metabolite. Results of a pharmacokinetics study suggest that itraconazole may undergo saturable metabolism with multiple dosing. Fecal excretion of the parent drug varies between 3 to 18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 40% of the dose is excreted as inactive metabolites in the urine. No single excreted metabolite represents more than 5% of a dose. Itraconazole total plasma clearance averaged 381 ± 95 mL/min following intravenous administration.

#### **Special Populations:**

Renal Insufficiency: Plasma concentrations of itraconazole in patients with mild to severe renal insufficiency, including patients receiving hemodialysis, were comparable to those obtained in healthy subjects.

Hepatic Insufficiency: The effect of hepatic impairment on the plasma concentrations of itraconazole is unknown. It is recommended that patients with hepatic impairment be carefully monitored when taking itraconazole.

## INDICATIONS AND USAGE

Itraconazole capsules are indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

1. Blastomycosis, pulmonary and extrapulmonary;
2. Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; and
3. Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Itraconazole capsules are also indicated for the treatment of the following fungal infections in non-immunocompromised patients:

1. Onychomycosis of the toenail with or without fingernail involvement due to dermatophytes (tinea unguium).
2. Onychomycosis of the fingernail due to dermatophytes (tinea unguium).

Specimens for fungal cultures and other relevant laboratory studies (wet mount, histopathology, serology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

### **Description of Clinical Studies:**

*Blastomycosis:* Analyses were conducted on data from two open-label, non-concurrently controlled studies (n=73 combined) in patients with normal or abnormal immune status. The median dose was 200 mg/day. A response for most signs and symptoms was observed within the first two weeks, and all cleared between 3 and 6 months. Results of these two studies demonstrated substantial evidence of the effectiveness of itraconazole, for the treatment of blastomycosis, compared to the natural history of untreated cases.

*Histoplasmosis:* Analyses were conducted on data from two open-label, non-concurrently controlled studies (n=34 combined) in patients with normal or abnormal immune status (not including HIV-infected patients). The median dose was 200 mg/day. A response for most signs and symptoms was observed within the first 2 weeks, and all cleared between 3 and 12 months. Results of these two studies demonstrated substantial evidence of the effectiveness of itraconazole, for the treatment of histoplasmosis, compared to the natural history of untreated cases.

*Histoplasmosis in HIV-infected patients:* Data from a small number of HIV-infected patients suggested that the response rate of histoplasmosis in HIV-infected patients is similar to non-HIV-infected patients. The clinical course of histoplasmosis in HIV-infected patients is more severe and usually requires maintenance therapy to prevent relapse.

*Aspergillosis:* Analyses were conducted on data from an open-label, "single-patient-use" protocol designed to make itraconazole available in the U.S. for patients who either failed or were intolerant to amphotericin B therapy (n=190). The findings were corroborated by two smaller open-label studies (n=31 combined) in the same patient population. Most adult patients were treated with a daily dose of 200 mg to 400 mg with a median duration of 3 months. Results of these studies demonstrated substantial evidence of effectiveness of itraconazole, as a second-line therapy for the treatment of aspergillosis, compared to the natural history of the disease in patients who either failed or were intolerant to amphotericin B therapy.

*Onychomycosis of the toenail:* Analyses were conducted on data from three double-blind, placebo-controlled studies (n=214 total; 110 given itraconazole capsules) in which patients with onychomycosis of the toenails received 200 mg qd for 12 consecutive weeks. Results of these studies demonstrated mycological cure, defined as simultaneous occurrence of negative KOH plus negative culture, in 54% of patients. Thirty-five percent (35%) of patients were considered an overall success (mycological cure plus clear or minimal nail involvement with significantly decreased signs) and 14% of patients demonstrated mycological cure plus clinical cure (clearance of all signs, with or without residual nail deformity). The mean time to overall success was approximately 10 months. Twenty-one percent (21%) of the overall success group had a relapse (worsening of the global score or conversion of KOH or culture from negative to positive).

*Onychomycosis of the fingernail:* Analyses were conducted on data from a double-blind, placebo-controlled study (n=73 total; 37 given itraconazole capsules) in which patients with onychomycosis of the fingernails received two pulses of 200 mg of itraconazole bid for one week separated by a 3 week period without itraconazole. Results demonstrated mycological cure in 61% of patients. Fifty-six percent (56%) of patients were considered an over success and 47% of patients demonstrated mycological cure plus clinical cure. The mean time to overall success was approximately 5 months. None of the patients who achieved overall success relapsed.

## CONTRAINDICATIONS

Coadministration of itraconazole capsules with certain drugs metabolized by the P450 3A enzyme system may result in increased plasma concentrations of those drugs leading to potentially serious and/or life-threatening adverse events. Terfenadine, astemizole, oral triazolam, oral midazolam and cisapride are specifically contraindicated with itraconazole. HMG-CoA reductase inhibitors metabolized by this system (e.g., lovastatin and simvastatin) should also be discontinued during itraconazole therapy. (See PRECAUTIONS - Drug Interactions.)

Itraconazole should not be administered for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy.

Itraconazole capsules are contraindicated in patients who have shown hypersensitivity to the drug or its excipients. There is no information regarding cross hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing itraconazole to patients with hypersensitivity to other azoles.

## **WARNINGS**

Itraconazole capsules and itraconazole oral solution should not be used interchangeably. This is because drug exposure is greater with the oral solution than with the capsules when the same dose of drug is given. Additionally, the topical effects of mucosal exposure may be different between the two formulations. Only the oral solution has been demonstrated effective for oral and/or esophageal candidiasis.

### **Hepatitis:**

There have been rare cases of reversible idiosyncratic hepatitis reported among patients taking itraconazole capsules. Itraconazole has been associated with rare cases of serious hepatotoxicity, including fatalities, primarily in patients with serious underlying medical conditions taking multiple medications. The causal association with itraconazole is uncertain. If clinical signs and symptoms develop that are consistent with liver disease and may be attributable to itraconazole, itraconazole capsules should be discontinued.

### **Cardiac Dysrhythmias:**

There have been rare cases of life-threatening cardiac dysrhythmia and death reported in patients receiving terfenadine and itraconazole. Coadministration of terfenadine, astemizole and cisapride with itraconazole is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and PRECAUTIONS - Drug Interactions.)

## **PRECAUTIONS**

### **General:**

Hepatic enzyme test values should be monitored in patients with preexisting hepatic function abnormalities. Hepatic enzyme test values should be monitored periodically in all patients

receiving continuous treatment for more than one month or at any time a patient develops signs or symptoms suggestive of liver dysfunction.

Itraconazole capsules should be administered after a full meal. (See CLINICAL PHARMACOLOGY - Pharmacokinetics and Metabolism.)

Under fasted conditions, itraconazole absorption was decreased in the presence of decreased gastric acidity. The absorption of itraconazole may be decreased with the concomitant administration of antacids or gastric acid secretion suppressors. Studies conducted under fasted conditions demonstrated that administration with 8 ounces of a cola beverage resulted in increased absorption of itraconazole in AIDS patients with relative or absolute achlorhydria. This increase relative to the effects of a full meal is unknown. (See CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism.)

#### **Information For Patients:**

Patients should be aware that itraconazole capsules is a different preparation than itraconazole oral solution, and these should not be used interchangeably. This is because drug exposure is greater with the oral solution than with the capsules when the same dose of drug is given. Additionally, the topical effects of mucosal exposure may be different between the two formulations. Only the oral solution has been demonstrated effective for oral and/or esophageal candidiasis.

Patients should be instructed to take itraconazole with a full meal.

Patients should be instructed to report any signs and symptoms that may suggest liver dysfunction so that the appropriate laboratory testing can be done. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine or pale stool.

Patients should be instructed to contact their physician before taking any concomitant medications with itraconazole to insure there are no potential drug interactions.

#### **Drug Interactions:**

Both itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of the cytochrome P450 3A enzyme system. Coadministration of itraconazole and drugs primarily metabolized by the cytochrome P450 3A enzyme system may result in increased plasma concentrations of the other drug that could increase or prolong both its therapeutic and adverse effects. Therefore, unless otherwise specified, concomitant medications metabolized by the P450 3A enzyme system should be discontinued as medically indicated.

#### **Table of Selected Drugs That Are Predicted to Have Plasma Concentrations Increased by Itraconazole<sup>+</sup>**

<p><i>Anticoagulants:</i> warfarin</p> <p><i>Antihistamines:</i> terfenadine<sup>*</sup>, astemizole<sup>*</sup></p> <p><i>Anti-HIV protease inhibitors:</i> ritonavir, indinavir</p> <p><i>Antineoplastic agents:</i> vinca alkaloids</p> <p><i>Benzodiazepines:</i> midazolam<sup>*,†</sup>, triazolam<sup>*</sup>, diazepam</p> <p><i>Calcium channel blockers:</i> dihydropyridines</p> <p><i>Cholesterol-lowering agents:</i> lovastatin<sup>*</sup>, simvastatin<sup>*</sup></p> <p><i>GI motility agents:</i> cisapride<sup>*</sup></p> <p><i>Immunosuppressive agents:</i> cyclosporine, tacrolimus</p> <p><i>Steroids:</i> methylprednisolone</p> <p><i>Other:</i> digoxin, quinidine</p>
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<sup>+</sup>This table is not all inclusive.

<sup>\*</sup>Specifically contraindicated with itraconazole based on clinical and/or pharmacokinetics studies (see WARNINGS and below).

<sup>†</sup>See paragraph below on *Benzodiazepines* for information on parenteral administration.

#### **Table of Selected Drugs That Are Predicted to Decrease Itraconazole Plasma Concentrations<sup>+,‡</sup>**

<p><i>Anticonvulsants:</i> phenytoin, phenobarbital, carbamazepine</p> <p><i>Antimycobacterial agents:</i> isoniazid, rifampin, rifabutin</p>
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<sup>+</sup>This table is not all inclusive.

<sup>‡</sup>Itraconazole may not be effective due to decreased itraconazole plasma concentrations in patients using these agents concomitantly.

*Anticoagulants:* It has been reported that itraconazole enhances the anticoagulant effect of coumarin-like drugs. Therefore, prothrombin time should be carefully monitored in patients receiving itraconazole and coumarin-like drugs simultaneously.

*Anticonvulsants:* Reduced plasma concentrations of itraconazole were reported when itraconazole was coadministered with phenytoin. The physician is advised to monitor the plasma concentrations of itraconazole when phenytoin is taken concurrently, and to increase the dose of itraconazole if necessary.

*Antihistamines:* Coadministration of terfenadine with itraconazole has led to elevated plasma concentrations of terfenadine, resulting in rare instances of life-threatening cardiac dysrhythmia and death. Coadministration of astemizole with itraconazole has led to elevated plasma concentrations of astemizole and desmethylastemizole which may prolong the QT intervals.

Therefore, concomitant administration of itraconazole with astemizole is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

*Anti-HIV protease inhibitors:* Coadministration of itraconazole with protease inhibitors primarily metabolized by the cytochrome P450 3A enzyme system, such as ritonavir or indinavir, may result in changes in plasma concentrations of both drugs. Caution is advised when these drugs are used concomitantly.

*Anti-HIV reverse transcriptase inhibitors:* The results from a study in which eight HIV-infected individuals were treated with zidovudine,  $8 \pm 0.4$  mg/kg/day, showed that the pharmacokinetics of zidovudine were not affected during concomitant administration of itraconazole capsules, 100 mg bid. Other agents have not been studied.

*Antimycobacterial agents:* Plasma concentrations of azole antifungal agents are reduced when given concurrently with isoniazid or rifampin. Alternative antifungal therapy should be considered if isoniazid or rifampin is necessary. A similar effect may be expected with rifabutin.

*Antineoplastic agents:* The metabolism of vinca alkaloids may be inhibited by itraconazole. Therefore, patients receiving itraconazole concomitantly with vinca alkaloids should be monitored for an increase and/or prolongation of the effects of the latter drug product, including adverse effects such as peripheral neuropathy and ileus, and the dose of the vinca alkaloid should be adjusted appropriately.

*Benzodiazepines:* Coadministration of itraconazole with oral midazolam or triazolam has resulted in elevated plasma concentrations of the latter two drugs. This may potentiate and prolong hypnotic and sedative effects. These agents should not be used in patients treated with itraconazole. If midazolam is administered parenterally, special precaution and patient monitoring is required since the sedative effect may be prolonged. (See CONTRAINDICATIONS.)

Calcium channel blockers: Edema has been reported in patients concomitantly receiving itraconazole and dihydropyridine calcium channel blockers. Appropriate dosage adjustments may be necessary.

Cholesterol-lowering agents: Human pharmacokinetic data indicate that itraconazole inhibits the metabolism of lovastatin resulting in significantly elevated plasma concentrations of lovastatin or lovastatin acid, which have been associated with rhabdomyolysis. Use of HMG-CoA reductase inhibitors metabolized by the P450 3A enzyme system, such as lovastatin or simvastatin, should be temporarily discontinued during itraconazole therapy. (See CONTRAINDICATIONS.)

Digoxin: Coadministration of itraconazole and digoxin has led to increased plasma concentrations of digoxin. Digoxin concentrations should be monitored at the initiation of itraconazole therapy and frequently thereafter, and the dose of digoxin should be adjusted appropriately.

GI motility agents: Human pharmacokinetic data indicate that oral ketoconazole potently inhibits the metabolism of cisapride resulting in significantly elevated plasma concentrations of cisapride. Data suggest that coadministration of oral ketoconazole and cisapride can result in prolongation of the QT interval on the ECG. *In vitro* data suggest that itraconazole also markedly inhibits the biotransformation system mainly responsible for the metabolism of cisapride; therefore, concomitant administration of itraconazole with cisapride is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

H<sub>2</sub> antagonists: Reduced plasma concentrations of itraconazole were reported when itraconazole was coadministered with H<sub>2</sub> antagonists.

Immunosuppressive agents: Coadministration of itraconazole and cyclosporine or tacrolimus has led to increased plasma concentrations of the latter two agents. Cyclosporine and tacrolimus concentrations should be monitored at the initiation of itraconazole therapy and frequently thereafter, and the dose of cyclosporine or tacrolimus should be adjusted appropriately.

Oral hypoglycemic agents: Severe hypoglycemia has been reported in patients concomitantly receiving azole antifungal agents and oral hypoglycemic agents. Blood glucose concentrations should be carefully monitored when itraconazole and oral hypoglycemic agents are coadministered.

Quinidine: Tinnitus and decreased hearing have been reported in patients concomitantly receiving itraconazole and quinidine.

Steroids: The metabolism of methylprednisolone may be inhibited by itraconazole. Therefore, patients receiving itraconazole concomitantly with methylprednisolone should be monitored for an increase and/or prolongation of the effects of the latter drug product, including adverse effects, and the dose of methylprednisolone should be adjusted appropriately.

**Carcinogenesis, Mutagenesis, Impairment Of Fertility:**

Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels up to 80 mg/kg/day [approximately 10x the maximum recommended human dose (MRHD)]. Male rats treated with 25 mg/kg/day (3.1 x MRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolemia, which is a response of rats, but not dogs or humans, to chronic itraconazole administration. Female rats treated with 50 mg/kg/day (6.25 x MRHD) had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.

Itraconazole produced no mutagenic effects when assayed in a DNA repair test (unscheduled DNA synthesis) in primary rat hepatocytes, in Ames tests with *Salmonella typhimurium* (six strains) and *Escherichia coli*, in the mouse lymphoma gene mutation tests, in a sex-linked recessive lethal mutation (*Drosophila melanogaster*) test, in chromosome aberration tests in human lymphocytes, in a cell transformation test with C3H/10T<sub>1/2</sub> C18 mouse embryo fibroblasts cells, in a dominant lethal mutation test in male and female mice, and in micronucleus tests in mice and rats.

Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels of up to 40 mg/kg/day (5 x MRHD) even though parental toxicity was present at this dosage level. More severe signs of parental toxicity, including death, were present in the next higher dosage level, 160 mg/kg/day (20 x MRHD).

**Pregnancy:**

Teratogenic Effects, Pregnancy Category C: Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity and teratogenicity in rats at dosage levels of approximately 40 to 160 mg/kg/day (5-20 x MRHD) and in mice at dosage levels of approximately 80 mg/kg/day (10 x MRHD). In rats, the teratogenicity consisted of major skeletal defects; in mice it consisted of encephaloceles and/or macroglossia.

There are no studies in pregnant women. Itraconazole should be used for the treatment of systemic fungal infections in pregnancy only if the benefit outweighs the potential risk. Itraconazole should not be administered for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy. Itraconazole should not be administered to women of child-bearing potential for the treatment of onychomycosis unless they are taking effective measures to prevent pregnancy and the patient begins therapy on the second or third day following the onset of menses. Effective contraception should be continued throughout itraconazole therapy and for 2 months following the end of treatment.

**Nursing Mothers:**

Itraconazole is excreted in human milk; therefore, the expected benefits of itraconazole therapy

for the mother should be weighed against the potential risk from exposure of itraconazole to the infant. The U.S. Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breast-feed to avoid potential transmission of HIV to uninfected infants.

**Pediatric Use:**

The efficacy and safety of itraconazole have not been established in pediatric patients. No pharmacokinetic data are available in children. A small number of patients age 3 to 16 years have been treated with 100 mg/day of itraconazole for systemic fungal infections and no serious unexpected adverse effects have been reported. Itraconazole oral solution (5 mg/kg/day) has been administered to pediatric patients (n=26, age 0.5-12 years) for two weeks and no serious unexpected adverse events were reported.

In three toxicology studies using rats, itraconazole induced bone defects at dosage levels as low as 20 mg/kg/day (2.5 x MRHD). The induced defects included reduced bone plate activity, thinning of the zona compacta of the large bones and increased bone fragility. At a dosage level of 80 mg/kg/day (10 x MRHD) over one year or 160 mg/kg/day (20 x MRHD) for six months, itraconazole induced small tooth pulp with hypocellular appearance in some rats. While no such bone toxicity has been reported in adult patients, the long term effect of itraconazole in pediatric patients is unknown.

**HIV-infected Patients:**

Because hypochlorhydria has been reported in HIV-infected individuals, the absorption of itraconazole in these patients may be decreased.

**ADVERSE REACTIONS**

There have been rare cases of reversible idiosyncratic hepatitis reported among patients taking itraconazole capsules. Itraconazole has been associated with rare cases of serious hepatotoxicity, including fatalities, primarily in patients with serious underlying medical conditions taking multiple medications. The causal association with itraconazole is uncertain. If clinical signs and symptoms develop that are consistent with liver disease and may be attributable to itraconazole, itraconazole should be discontinued. (See WARNINGS.)

**Onychomycosis of the Toenail (Continuous dosing regimen of 200 mg qd for 12 consecutive weeks):**

Adverse events in the following table led to either temporary or permanent discontinuation of treatment:

Body System/Adverse Event	Incidence (%) (n=112)
Elevated Liver Enzymes (>2x normal range)	4%
Gastrointestinal Disorders	4%
Rash	3%
Hypertension	2%
Orthostatic Hypotension	1%
Headache	1%
Malaise	1%
Myalgia	1%
Vasculitis	1%
Vertigo	1%

Adverse events reported with an incidence of >1% in patients given itraconazole (200 mg qd for 12 consecutive weeks; n=112) in clinical trials of toenail onychomycosis were: headache (11; 10%), rhinitis (10; 9%), upper respiratory tract infection (9; 8%), sinusitis (8; 7%), injury (8; 7%), diarrhea (5; 4%), dyspepsia (5; 4%), flatulence (5; 4%), abdominal pain (4; 4%), dizziness (4; 4%), rash (4; 4%), nausea (3; 3%), cystitis (3; 3%), urinary tract infection (3; 3%), liver function abnormality (3; 3%), myalgia (3; 3%), appetite increased (2; 2%), constipation (2; 2%), gastritis (2; 2%), gastroenteritis (2; 2%), pharyngitis (2; 2%), asthenia (2; 2%), fever (2; 2%), pain (2; 2%), tremor (2; 2%), herpes zoster (2; 2%), and abnormal dreaming (2; 2%).

**Onychomycosis of the Fingernail (Pulse regimen consisting of two one-week treatment periods with 200 mg bid separated by a 3 week period without itraconazole):**

Adverse events in the following table led to either temporary or permanent discontinuation of treatment:

Body System/Adverse Event	Incidence (%) (n=37)
Rash/pruritus	3%
Hypertriglyceridemia	3%

Adverse events reported with an incidence of >1% in patients given itraconazole (two one-week treatment periods with 200 mg bid, separated by a 3 week period without itraconazole; n=37) in the clinical trial of fingernail onychomycosis were: headache (3; 8%), pruritus (2; 5%), nausea (2; 5%), rhinitis (2; 5%), rash (1; 3%), bursitis (1; 3%), anxiety (1; 3%), depression (1; 3%), constipation (1; 3%), abdominal pain (1; 3%), dyspepsia (1; 3%), ulcerative stomatitis (1; 3%), gingivitis (1; 3%), hypertriglyceridemia (1; 3%), sinusitis (1; 3%), fatigue (1; 3%), malaise (1; 3%), pain (1; 3%), injury (1; 3%).

**Systemic Fungal Infections:**

Adverse experience data in the following table are derived from 602 patients treated for systemic fungal disease in U.S. clinical trials, who were immunocompromised or receiving multiple concomitant medications. Of these patients, treatment was discontinued in 10.5% of patients due to adverse events. The median duration before discontinuation of therapy was 81 days, with a range of 2 to 776 days. The table lists adverse events reported by at least 1% of patients.

Body System/Adverse Event (Incidence ≥ 1%)	Incidence (%)
Gastrointestinal disorders	
Nausea	10.6
Vomiting	5.1
Diarrhea	3.3
Abdominal pain	1.5
Anorexia	1.2

Body as a whole	
Edema	3.5
Fatigue	2.8
Fever	2.5
Malaise	1.2
Skin and appendages disorders	
Rash	8.6*
Pruritis	2.5
Central/peripheral nervous system	
Headache	3.8
Dizziness	1.7
Psychiatric disorders	
Libido decreased	1.2
Somnolence	1.2
Cardiovascular disorders	
Hypertension	3.2
Metabolic and nutritional disorders	
Hypokalemia	2.0
Urinary system disorders	
Albuminuria	1.2
Liver and biliary system disorders	
Hepatic function abnormal	2.7
Reproductive disorders, male	
Impotence	1.2

\* Rash tends to occur more frequently in immunocompromised patients receiving immunosuppressive medications.

Adverse events infrequently reported in all studies included: constipation, gastritis, depression, insomnia, tinnitus, menstrual disorder, adrenal insufficiency, gynecomastia and male breast pain.

In worldwide postmarketing experience with itraconazole capsules, allergic reactions including rash, pruritus, urticaria, angioedema and in rare instances, anaphylaxis and Stevens-Johnson syndrome, have been reported. Marketing experiences have also included reports of elevated liver enzymes and rare hepatitis. Although the causal association with itraconazole is uncertain, rare alopecia, hypertriglyceridemia, neutropenia and isolated cases of neuropathy have also been reported.

## OVERDOSAGE

Itraconazole is not removed by dialysis. In the event of accidental overdosage, supportive measures, including gastric lavage with sodium bicarbonate, should be employed.

There are limited data on the outcomes of patients ingesting high doses of itraconazole. In patients taking either 1000 mg of itraconazole oral solution or up to 3000 mg of itraconazole capsules, the adverse event profile was similar to that observed at recommended doses.

## DOSAGE AND ADMINISTRATION

Itraconazole capsules should be taken with a full meal to ensure maximal absorption.

**Treatment of blastomycosis and histoplasmosis:** The recommended dose is 200 mg once daily (2 capsules). If there is no obvious improvement or there is evidence of progressive fungal disease, the dose should be increased in 100 mg increments to a maximum of 400 mg daily. Doses above 200 mg per day should be given in two divided doses.

**Treatment of aspergillosis:** A daily dose of 200 mg to 400 mg is recommended.

**In life-threatening situations:** Although these studies did not provide for a loading dose, it is recommended, based on pharmacokinetic data, that a loading dose of 200 mg (2 capsules) tid (600 mg/day) be given for the first three days.

Treatment should be continued for a minimum of three months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. The above recommendations for the treatment of blastomycosis and histoplasmosis are based on the results of two open-label studies of patients with blastomycosis (n=73) and histoplasmosis (n=34) where results were compared to the expected outcome for untreated patients from historical controls. The recommendation for the treatment of aspergillosis is based primarily on the results of an open-label, single-patient use protocol designed to make itraconazole available in the U.S. for patients who either failed or were intolerant to amphotericin B therapy (n=190), and is supported by two smaller open-label studies (n=31 combined) in the same patient population.

**Onychomycosis:** Toenails with or without fingernail involvement: The recommended dose is 200 mg (2 capsules) qd for 12 consecutive weeks. Fingernails only: The recommended dosing regimen is two treatment pulses, each consisting of 200 mg (2 capsules) bid (400 mg/day) for one week. The pulses are separated by a 3-week period without itraconazole.

Itraconazole capsules and itraconazole oral solution should not be used interchangeably. Only the oral solution has been demonstrated effective for oral and/or esophageal candidiasis.

## HOW SUPPLIED

- Established Name
- Strength of dosage form
- Packaging, NDC number
- Dosage form, shape, color, imprinting
- Store at controlled room temperature 15° - 30°C (59° - 86°F). Protect from light and moisture.
- Dispense in a tight, light-resistant container.

**Include the following information at the end of the HOW SUPPLIED section:**

- Date of latest revision.
- “Manufactured by” statement. - Should be consistent with container labels and/or carton labeling.

## CONTAINER LABEL

In addition to the general label requirements (“Rx only” statement, statement of net quantity, etc.) please include the following:

Main Panel:

- The established name and strength should read as follows:

ITRACONAZOLE CAPSULES

100 mg

- We recommend that “Rx only” appear prominently on the principal display panel.

Side Panel:

- Each capsule contains: Itraconazole 100 mg
- Usual Dosage: See package insert.
- Store at controlled room temperature 15° - 30°C (59° - 86°F). Protect from light and moisture.